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DETAILED ACTION

Claims 1-19 are pending in this application.

Claim Objections

Claim 15 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim must refer to other claims in the alternative only. See MPEP § 608.01(n). Claim 15 refers to “claims 13 or 14” and also to "claim 1".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compound of formula I or a pharmaceutically acceptable salt thereof, does not reasonably provide enablement for **hydrates** or **solvates** thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples,

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6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that “undue experimentation” would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claims recite “A compound ... and the pharmaceutically acceptable salts, **hydrates, solvates** ... thereof” wherein there is insufficient description in the specification regarding the types of ‘hydrates’ or ‘solvates’ intended by the recitation.

The specification provides that ‘solvates are the compounds of the invention with solvents’ (see page 7). In general ‘**solvate**’ is ‘a compound formed with one or more solvent molecules’; the specification, however, has no working examples of a “hydrate” or “solvate” of the compound of instant claims. As per the synthesis provided for the instant compound or the salt thereof, the compound was in contact with solvents and/or water, yet the specification does not disclose that the synthesis resulted in the formation of a hydrate or solvate. The specification does not report any hydrates or solvates of the compound or its salts, as evident from spectral data provided for these compounds.

Searching the pertinent art in the related pyrimidine area did not result in support for such solvates of instant pyrimidine compounds. Searching the more general area of solvates resulted in pertinent reference West applied below. West clearly shows lack of predictability of the art in the solvate area.

Based on these two facts, a scope of enablement rejection follows using relevant Wands factors. Hence, the burden of establishing the *prime facie* case is met with.

(i). **The nature of the invention and the state of the prior art:**

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Specification is not adequately enabled as to how to make hydrate or solvate of the claimed compounds and the specification has no example of hydrate or solvate of the instant compounds. The instant claim includes the compound, salts thereof and therefore, includes a considerably large number of compounds and there is no teaching of any hydrate or solvate for these compounds.

Search in the pertinent art, including water as solvent resulted in a pertinent reference, which is indicative of unpredictability of hydrate or solvate formation in general. The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is the compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometry of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stable region of the solvate. In the instant case of solvate, a similar reasoning therefore applies. Water is a solvent and hence it is held that a pertinent detail of West, which relates to solvates, is also applicable to water.

In addition, an additional search resulted in Vippagunta et al., Advanced Drug Delivery Reviews 48: 3-26, 2001, which clearly states that formation of solvates is unpredictable. See

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entire document especially page 18, right column section 3.4. Note Vippagunta et al., states “Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for series of related compounds”.

Joachim Ulrich (Kirk-Othmer Encyclopedia of Chemical Technology) provides that “Pseudopolymorphs are solvates or in the case of water as solvent, hydrates, which means crystals that incorporate solvent molecules into the crystal lattice. Pseudopolymorphs exhibit different crystal forms and/or different densities, solubilities, dissolution rates, colors, hardnesses, etc. Compared with polymorphs, there is an additional degree of freedom (than temperature and pressure), which means a different solvent or even the moisture of the air that might change the stable region of the pseudopolymorph”.

(ii). **The predictability or lack thereof in the art:**

Hence the solvate as applied to the above-mentioned compounds claimed by the applicant are not art-recognized compounds and hence there should be adequate enabling disclosure in the specification with working example(s).

(iii). **The amount of direction or guidance present:**

Examples illustrated in the experimental section are limited to making the compounds not related to solvates. There is no example of solvate of instant compound. The synthetic examples of the compound or the corresponding salts were shown in the specification to have come in contact with water and/or other solvent but there is showing that these compounds formed solvates. Hence it is clear that merely bringing the compound and water or solvent together does not result in solvate and additional direction or guidance is needed to make them - specification has no such direction or guidance.

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(iv). **The presence or absence of working examples:**

There is no working example of any solvate or hydrate formed. The claims are drawn to hydrate and solvate, yet the numerous examples presented all failed to produce a solvate or hydrate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 “[T]he specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there, is no evidence that such compounds exist... the examples of the patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist.” The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, there should be showing supporting that hydrates or solvates of these compounds exist and therefore can be made.

(v). **The breadth of the claims & the quantity of experimentation needed:**

The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of experimentation, supported by state of the art references establishing the unpredictability of formation of hydrates and solvates, there is no guarantee that one would get the product of desired **hydrate** or **solvate** of the claimed compound.

2. Claims 14 and 17-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition containing the compound of formula (I) and a pharmaceutically acceptable diluent; or a method of treating acute myocardial infarction, does not reasonably provide enablement for a composition for the treatment of acute and chronic

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inflammatory, ischaemic and/or remodeling processes; or a method of treating acute and chronic inflammatory, ischaemic or remodeling processes generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that “undue experimentation” would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

Claim 14 is directed to 'a composition for the treatment of acute and chronic inflammatory, ischaemic and/or remodeling processes', and the specification does not sufficiently enable the entire scope of the use recited for the pharmaceutical composition, for the reasons provided above. When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See MPEP § 2164.01(c). In contrast, when a compound or composition claim is **not** limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for non-enablement based on how to use.

The instant claims 17-19 are drawn to “use of the compounds for the treatment of acute and chronic inflammatory, ischaemic or remodeling processes”. As per the specification, the

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instant compounds show human neutrophil elastase (HNE) inhibitory activity and are therefore useful in the treatment of diseases associated with HNE activity, which include acute and chronic inflammatory processes. First, the instant claims appear to be 'reach through' claims. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through to the corresponding therapeutic method of any or all diseases, disorders or conditions, for which they lack written description and enabling disclosure in the specification thereby requiring undue experimentation for one of skill in the art to practice the invention.

The testing assays are provided in the specification at pages 28-32 are to test the activity of the compounds as HNE inhibitors, however, there is insufficient guidance in the disclosure regarding the provided assay. There is no data for any of the instantly claimed compounds. There is no indication that the test results provide the necessary data required for the treatment of assorted diseases of the instant claims. Further, applicant has not provided how the test data correlates with the efficacy of the compounds in the treatment of all types of diseases encompassed by the instant methods.

Enablement for the scope of "inflammation" or "inflammatory processes or diseases" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process, which can take place individually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly,

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treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally. Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neurophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages, which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters. Otitis media is an inflammation of the lining of the middle ear and is commonly caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics. Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and

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naproxen) along with muscle relaxants can be used in the non-bacterial cases. The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammation. It establishes that it is not reasonable to any agent to be able to treat inflammation generally.

'Cardiovascular diseases' embrace a vast array of problems, many of which are contradictory to others. Thus, it covers hypertension and hypotension. It covers various types of arrhythmias; angina pectoris', the thrombotic symptoms of diabetes, atherosclerosis and hyperlipoproteinaemias, ischemic heart disease including congestive heart failure and myocardial infarction, stroke, and peripheral vascular disorders, such as deep-vein thrombosis and thrombophlebitis percutaneous transluminal coronary angiography (PTCAI; elevated blood levels of triglycerides, of total cholesterol or of LDL cholesterol, arteriosclerosis, peripheral vascular disease, cerebral vascular disease and pulmonary hypertension, migraine, cardiomyopathy, etc. Not one compound -- let alone a genus of trillions of compounds, could possibly be effective against such disorders generally. However, the instant claim includes disorders that are known to exist and those that may be discovered in the future and therefore, is extremely broad. For example, regarding arteriosclerosis, a state of the art online reference states "the relationship between blood cholesterol levels and arteriosclerosis is not fully understood" (see <http://www.infoplease.com/ce6/sci/A0804864.html>).

By way of the HNE inhibiting activity, the instant compounds are claimed to be useful in treating various types of disorders. However, there is no nexus in the specification how this activity relates to all types of diseases of the claims, such as chronic obstructive pulmonary disease, acute coronary syndrome, acute myocardial infarction, development of heart failure, etc.

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See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, and the data provided is insufficient for one of ordinary skill in the art in order to extrapolate to the other methods of treatment of the claims. It is inconceivable as to how the claimed compounds can treat the extremely difficult diseases embraced by the instant claims.

There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein and therefore, require the treatment. Next, applicant's attention is drawn to the "Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001" wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly intended therapeutic and preventive methods solely based on the insulin secretion stimulating activity disclosed for the compounds.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

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Thus, factors such as “sufficient working examples”, “the level of skill in the art” and “predictability”, etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. In the claims the plural recitation “Compounds ...” is not proper claim language. The form of the claim can be improved by replacing the above recitation by: -- A compound -
-.
2. Each of claims 5-10 refer to “Compounds of formula (I)”, however, the claims do not contain the structural formula (I) within the claims. A claim to be independent must contain all limitations within the claim or should depend from a claim containing the limitations.

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3. Claim 11 recites that "R¹, R³, R⁴ and R⁶ have the meaning indicated in any of the preceding claims", however, does not specifically indicate a specific claim for the meanings of the variables.
4. Claim 16-18 provide for the use of the compounds, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 101

Claims 16-18 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

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Claims 1-19 are rejected under 35 U.S.C. 102(e) as being anticipated by Gielen et al., WO 2004/024700 (International filing date: August 28, 2003). The instant claims read on reference disclosed compounds, see the structural formula (I) in page 3 and the corresponding compounds of the examples. The compounds are taught to be useful as pharmaceutical agents for the treatment of chronic obstructive pulmonary diseases, see the abstract.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention “by another,” or by an appropriate showing under 37 CFR 1.131.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

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Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-19 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over pending claims of each of copending Applications No. 10/590,786 or 10/527,391 (both applications now allowed). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims substantially overlap the compounds of the reference claims, see the claims in each of the application. It would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the compounds from the reference claims and/or use the compounds in any of the methods taught by the reference, including those instantly claimed, because the skilled artisan would have had the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as pharmaceutical therapeutic agents. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Receipt is acknowledged of the Information Disclosure Statements filed on August 24, 2006 and April 8, 2008 and copies are enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Monday-Friday from 8:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

**/Deepak Rao/
Primary Examiner
Art Unit 1624**

November 14, 2009